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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/302,896	04/30/1999	MICHAEL B. CHANCELLOR	2710-4007-US	7603

28089 7590 07/09/2003

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EXAMINER
KAUSHAL, SUMESH

ART UNIT	PAPER NUMBER
1636	18

DATE MAILED: 07/09/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application N .	Applicant(s)	
	09/302,896	CHANCELLOR ET AL.	
	Examiner	Art Unit	
	Sumesh Kaushal Ph.D.	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

P ri d for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 April 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disp sition of Claims

4)☒ Claim(s) *119-195* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *119-195* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Applicant's response filed on 04/24/03 has been acknowledged.

Claims119-195 are newly filed.
Claims 119-195 are pending and are examined in this office action.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The references cited herein are of record in a prior Office action.

► *Applicants are advised to follow Amendment Practice under revised 37 CFR §1.121 (http://www.uspto.gov/web/offices/pac/dapp/opla/preognotice/revamdtprac.htm). Each amendment document that includes a change to an existing claim, or submission of a new claim,* ***must include a complete listing of all claims*** *in the application. After each claim number, the status must be indicated in a parenthetical expression, and the text of each claim under examination (with markings to show current changes) must be presented. The listing will serve to replace all prior versions of the claims in the application.*

Claim Rejections - 35 USC § 112

1. Claims 119-195 stand rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, **to make and/or use the invention** for the same reasons of record as set forth in the office action mailed on 10/24/02.

Nature Of Invention:

Invention relates to method of treating stress urinary incontinence (ex-vivo gene therapy).

Breadth Of Claims And Guidance Provided By The Inventor:

The instant claims are drawn to a method of treating urinary stress incontinence by repairing injured genitourinary tract tissue by administering genetically engineered muscle derived cells which encodes a bioactive molecule. The instant claims are further drawn to the method wherein the bioactive molecule is inducible nitric oxide synthase (iNOS) and/or a growth factor, wherein the growth factor is an insulin-like growth factor (IGF). In addition the claims are drawn to a method of repairing sphincter muscle injury or dysfunction by administering

muscle derived cells, wherein the cell are genetically engineered to contain nucleic acid encoding a heterologous bioactive gene product (growth factor, IGF).

The instant specification teaches the injection of genetically engineered GH8 myoblast cell line expressing b-galactosidase into the urethral wall of adult female rat with cryo-induced uretheral injury (page 54, example-2, table-1). The specification further teaches injection of the genetically engineered myoblast cells expressing b-galactosidase and iNOS into the dome of the bladder and into left and right lateral walls near the dome (page 57, example-3, table-2). The specification concluded that these experiments demonstrated an alteration of bladder and urethral function with cyro-injury model (spec. page 59, line 5). The specification further teaches the injection of myoblasts expression iNOS gene resulted in the release of NO at the site of injection site in penis and bladder but fails to disclose that release of NO resulted in the treatment of urinary stress incontinence especially in patients with afferent nerve induced micturition reflexes (spec. page 79, lines 14-24, *infra Young et al*). Similarly the specification teaches that IGF-1 promotes muscle growth in vitro, but fails to disclose that over expression of IGF-1 would lead to the treatment of the treatment of urinary stress incontinence especially in patients with afferent nerve induced micturition reflexes (spec. page 83, line 5, *infra Young et al).*

The scope of instant invention as claimed encompasses repairing any and all sites in the genitourinary tract tissue by injecting muscle derived cells which are genetically engineered to express any and all bioactive molecules, to improve or alleviate urinary stress incontinence.

- However, the instant specification fails to disclose that injection of genetically engineered MDCs into any and all sites of the genitourinary tract would lead to the treatment of urinary stress incontinence.
- The instant specification fails to disclose that that injection of any and all types of MDCs derived from any and all types of muscles into the genitourinary tract would lead to the treatment of urinary stress incontinence.
- The instant specification fails to disclose that injection of genetically engineered MDC expressing any and all bioactive compounds would lead to the treatment of urinary stress incontinence.

- The instant specification fails to disclose that injection of genetically engineered MDCs expressing any and all tropic factors (growth factors, especially IGF-1) would lead to the treatment of urinary stress incontinence.
- The instant specification fails to disclose that injection of genetically engineered MDCs expressing any and all immune suppression factor would lead to the treatment of urinary stress incontinence by allowing survival of injected cells and prevent an adverse immune response.
- The instant specification fails to disclose any method that repairs the sphincter muscle injury or dysfunction by introducing any and all types of muscle derived cells, wherein the cells are genetically engineered to produce any and all bioactive gene products.

State Of Art And Predictability:

The instant invention is drawn to a method that requires gene-based therapeutics. The Gene therapy is considered highly experimental area of research at this time, and both researchers and the public agree that demonstrable progress to date has fallen short of initial expectations. No cures can as yet be attributed to gene therapy. (Rosenberg et al, Science 287:1751, 2000, Verma, Mol. Ther. 1: 493, 2000, Friedmann, Science 287(5461):2163-5, 2000, Anderson WF, Nature 392:25-30, 1998; Verma et al Nature 389:239-242, 1997, Touchette, Nat. Med. 2(1) 7-8, 1996). None of the human studies to date has shown definite efficacy, despite more than 300 protocols involving 3000 patients since September 1990 (Anderson page 25 col.1 para.1). Most studies have neglected to include well-defined biochemical or clinical end points that would clearly indicate whether the therapy is having a desired effect. Furthermore, Recombinant DNA Advisory committee (RAC) also emphasized that expectations of current gene therapy protocols have been over sold without any apparent success (Touchette page 7, col.1 para. 2; page 8, col.2 para 1-4). The advisory panel further emphasized the need for a greater understanding of an underlying mechanism that contribute to a genetic disease along with the pathogenesis of the disease. (Touchette, page 7, col.3, para.3). In instant case the specification fails to disclose a method of treating urinary stress incontinence by repairing any and all sites in the genitourinary tract tissue by injecting any and all muscle derived cells wherein the muscle derive cells are genetically engineered to express any and all bioactive molecules.

The state of the art at the time of filing teaches that urinary stress incontinence occurs when urethral sphincter muscle is not sufficiently strong to prevent urine leakage for example while coughing or jumping. (Chancellor et al, TRENDS in Mol. Med. 7(7):301-306, 2001; see Spec. page 8, lines 15-28). Furthermore, in many patients the urinary incontinence the result of mixed urge and stress incontinence. The uretheral afferent nerve activity affects the micturition reflexes, indicating that in patients with stress urinary incontinence, the leakage of urine into proximal urethra stimulates afferent nerve, which facilitate voiding reflexes (Young et al, The Journal of Urology, 162:204-212, 1999, see abstract, conclusions). The instant specification fails to disclose a method that repairs spinchter muscle injury or dysfunction by introducing genetically engineered cells. Furthermore the specification fails to provide any guidance to treat urinary stress incontinence by modulating the afferent nerve reflexes in patients with mixed urge and stress incontinence conditions. Young et al clearly teaches that in patients with mixed stress and urge incontinence it would be appropriate to treat stress incontinence as a strategy to improve or cure detrusor instability (Young page 209, col.1, para.1). Therefore considering the instant specification, the applicant fails to disclose that bulking of the sphincter muscle alone would lead to the treatment of urinary stress incontinence, since the urinary stress incontinence is not only caused by the weakening of sphincter muscle but is also the result of afferent nerve reflexes. The state of the art at the time of filing clearly teaches that despite the gene therapy holds much promise to come, the success will only be achieved through continued rigorous research on the most fundamental mechanisms that contribute to a genetic disease along with the pathogenesis of the disease, gene delivery and gene expression in animal.

Response to arguments

The applicant argues that stress urinary incontinence can be treated by introducing MDC into tissue of genitourinary tract for example urethra or sphincter tissue. The applicant argues that representative publications serve to demonstrate that those in a pertinent art acknowledge and accept the use of MDC to affect repair of genitourinary tract injury or dysfunction such as urinary incontinence (response, page 22). The applicant argues that the urethral afferent nerve activity does not cause stress urinary incontinence, rather stress incontinence can induce or increase urethral afferent activity (response, page 23). The applicant argues that specification demonstrate that injected MDCs survive 30-60 days following introduction of cells in an animal.

The applicant argues that animals (cryo-induced uretheral injury) treated with MDCs demonstrate formation of new muscle tissues following injection and have improved bladder contractility (response, page 24). The applicant argues that MDC injection in uretheral wall modulates destrusor muscle contractility. The applicant argues that the expression of iNOS by implanted cells further enhances the treatment process (response page 24). The applicant further argues that as understood by a skilled practitioner in this art, bladder and urethra often serve as collocations for therapies and functional studies. The applicant concluded that MDC can be employed as non-allergenic and physiological agent to bulk up genitourinary tract muscle wall, thereby treating urinary incontinence as well as enhancing coaptation and improving the damage or injury to urinary sphincter, bladder and urethral muscle tissue (response, page 25).

However, this is found NOT persuasive. Applicant's argument alone cannot take place of evidence lacking in the record (see In re Scarbrough 182 USPQ, (CCPA) 1979). The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). In instant case treatment of urinary incontinence by gene based therapies that requires implantation of genetically engineered cells encoding any and all gene products is not considered routine in the art and without sufficient guidance to a specific MDC cell type, therapeutic gene of interest and a specific site of implantation of MDCs in the genitourinary tract, the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). At best the specification only teaches the treatment of urethral injury by injecting myoblasts (GH8) into the cyro-injured urethra of female rat (spec. page 54). The specification even fails disclose that injection of myoblast cells expressing iNOS provides any enhancements in the treatment process (see page 56, table-1; page 59, table-2). Furthermore the cryo-induced urethral injury does not represent the complexities found in patients with mixed urge and stress incontinence conditions, which not only involves urethral muscle functions but also nerve stimulation. In addition considering the unpredictability in the art the specification fails to disclose a single working example that establishes that injection of any MDCs type in the sphincter, detrusor or bladder muscle tissue would lead to the treatment of urinary incontinence. At best the references cited by the applicant demonstrated the survival of genetically engineered autologous muscle cells into the urethral tissue but fails to disclose that such an implantation of cell results in the

treatment of stress urinary incontinence (see Yokoyama et al, (1-3), references cited in response on pages 22-23). It is noted that the unpredictability of a particular area may alone provide reasonable doubt as to the accuracy of the broad statement made in support of enablement of claims. See Ex parte Singh, 17 USPQ2d 1714 (BPAI 1991). Therefore, one skill in the art would have to engage in excessive and undue amount of experimentation to exercise the invention as claimed.

2. Claims 119-195 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The term "muscle derived cells (MDCs)" is a relative term, which renders the claim indefinite. The term "muscle derived cell" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably ascertain of the scope of the invention. For example, it is unclear what constitutes a non-adherent, non-fibroblast, desmin-positive cell that have round morphology in this context, since desmin is know to express in all muscle cell types.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sumesh Kaushal Ph.D. whose telephone number is 703-305-6838. The examiner can normally be reached on Mon-Fri. from 9AM-5PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yucel Irem Ph.D. can be reached on 703-305-1998. The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-4242 for regular communications and 703-308-8724 for After Final communications. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

S. Kaushal
Patent examiner

JEFFREY FREDMAN
PRIMARY EXAMINER